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14. ABSTRACT The overall objective of this research program was to understand whether androgen deprivation therapy (ADT) decreases the quality of survival by amplifying age-related cognitive decline and increasing the risk for neurodegenerative disease. This report summarizes the entire study period. This study demonstrated the use of multiple forms of neuroimaging to examine potential neurotoxicity of ADT. Brain activity did not differ between men who were or were not on ADT. White matter integrity, particularly in the occipital region does appear to be lower in men on ADT. Quantitative T1 shows an expected age-related increase in both grey and white matter, but ADT does not affect this magnetic resonance measure of macromolecular content. Men on ADT did not meet the criteria for early Alzheimer's disease. While still in the clinically normal range, men on ADT reported more depression and more confusion than men who were not on ADT, and additional data (POMS, FAQ, FACT-P) suggest malaise is particularly difficult for the men early in ADT treatment.					
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INTRODUCTION:

The overall objective of this research program was to understand whether androgen deprivation therapy (ADT) decreases the quality of survival by amplifying age-related cognitive decline and increasing the risk for neurodegenerative disease. We compared measures of quality of life, memory, memory induced brain activity using fMRI, and tissue integrity using QT₁ neuroimaging methods in men on long versus short term treatment with ADT as well as men who are not on ADT.

BODY:

Only partial data and on only on some of the outcome measures has been reported in prior quarterly or annual reports. Thus, here we summarize final outcomes on all measures in the study.

Behavioral Findings: The behavioral findings were examined in two stages. First we examined whether men on ADT (N=21) differed from men with prostate cancer (PC) who were not on ADT (N=16). This provides an overall view of the effects of ADT. Subsequently we asked whether men early in the course of ADT (3-6 months; N=8) differed from those on long term ADT (>2 years; N=13) or men who were not on ADT (N=16). The groups were matched for age (age range 60-80), years of education (range 12-22 years), verbal intelligence (scaled scores 7-18), and a screening measure for dementia (score range 25-30; Mini Mental Status Exam (Folstein et al., 1983). None scored in the demented range. All analyses (ANOVA or post hoc tests) used a two-tailed significance level of $p < .05$. Where data was not normally distributed even with transformation (log or square root), nonparametric statistics were used.

Cognitive Measures

Geriatric Depression Scale (GDS; (Yesavage et al., 1983): Men on ADT report more depression than men who are not on ADT ($p < .01$) although their scores were *still within the normal range*, thus they would not qualify on this screening measures as clinically depressed. In the three group analysis (early-ADT, long-term ADT and No ADT), the groups differed ($p < .01$); men who were not on ADT were less depressed than the two other groups ($ps < .05$), who did not differ from each other ($ps > .10$; see Fig. 1). Thus, in subsequent analyses of behavioral measures, the scores on the depression scaled were used as a covariate and we mention whether this affected outcomes.

Memory - Paragraph Recall (Wechsler, 1987): ADT, nor length of treatment affected memory performance and covarying by GDS did not affect these results (all $ps > .10$; See Fig. 2). We note that this result is different than when men on ADT are compared to healthy men without prostate cancer (Green et al., 2002; Beer et al., 2006).

Memory – Word list learning: ADT, nor length of treatment affected word list learning or recognition performance and covarying by GDS did not affect these results (all $ps > .10$). This was true for word list encoding and recognition of targets words versus foils.

Cognitive Flexibility (Trail Making Test; (Tombaugh, 2004): ADT, nor length of treatment affected cognitive flexibility and covarying by GDS did not affect these results (all $ps > .10$). This was true for initial psychomotor speed (Trials A) as well as the cognitive flexibility portions of the measure (Trials B, and B-A; See Fig 3).

Quality of Life and Mood Measures

Mood (Profile of Mood States: (McNair et al., 1971): Overall, ADT did not affect scores on the fatigue, vigor, anger, tension or depression subscales and covarying for GDS scores did not modify these results ($p > .10$). However, but men on ADT reported significantly more confusion than men who were not on ADT ($p < .01$) and this remained significant when covaried for depression ($p < .05$). The three group analysis was also significant ($p < .01$), and posthoc analyses showed that men on ADT differed from those not on ADT ($p < .05$), but reports of confusion were comparable in men on long term versus early in ADT ($p > .10$ See Fig 4). Exploratory three group post hoc analyses did not find group differences in fatigue, vigor, anger or tension, however, men early in their ADT reported more depression than either men who were not on ADT or men on long term ADT ($p < .05$); men who were on long-term ADT did not differ from men who were not on ADT at all. For these analyses, data was missing for one man who was not on ADT.

The Memory functioning Questionnaire MFQ (Gilewski et al., 1990): ADT did not affect total or MFQ subscale scores, nor were there differences related to length of ADT ($p > .10$).

Pfeffer Functional Activities Questionnaire (FAQ: (Pfeffer et al., 1982; Tabert et al., 2002): ADT did not have an overall affect on the Pfeffer FAQ score ($p > .10$). However, there was a marginal main effect in the three group analysis ($p = .06$), and exploratory post hoc analyses showed that men who were early in their course of ADT had numerically higher FAQ scores, that were marginally significantly different than both men who were on long term ADT and those not on ADT ($p < .10$). Men who were not on ADT did not differ from those on long term ADT (see Fig 5).

Functional Assessment of Cancer Therapy-Prostate (FACT-P: Sullivan et al., 2007): Men on ADT reported poorer physical, functional and emotional well being than men who were not on ADT. These were marginally significant effects ($p < .08$) that were not significant when depression scores were used as covariates ($p > .50$) suggesting that physical, functional and emotional well being and GDS depression are assessing similar constructs. Whether complaints of physical or emotional well being are due to depression or visa versa cannot be determined by this study. Social well being scores on the Prostate Cancer Subscale did not differ between groups ($p > .10$). Together, overall quality of life (combining subscales) was marginally worse in men on ADT ($p = .05$). Exploratory analyses among the three groups showed that the significant ADT effects was solely due to the men early in their ADT treatment because in general, they had worse physical, functional, emotional well being, and overall quality of life than the men who were on long-term ADT and/or men who were not on ADT ($p \leq .05$; Fig 6), who did not differ from each other. Social well being did not differ among the three groups. This result should be contrasted with the GDS results alone, where men on ADT had higher depression scores regardless of length of treatment. This suggests that depression scores alone do not account for poor reports of quality of life in men early in ADT treatment.

Neuroimaging Measures:

Functional Magnetic Resonance Imaging (fMRI): We compared average signal change and peak signal during word list encoding and for those items subsequently remembered versus forgotten on a recognition test, between men on and not on ADT. There were no group differences on any measure in either left or right prefrontal or medial frontal cortex. However, signal differed based on the quality of the information to be remembered suggesting that the tasks were tapping the hypothesized brain regions for encoding and memory. For instance, words deeply encoded by having the subject make a determination as to whether an item was

human made or a natural object resulted in greater signal in the left prefrontal region during encoding than a judgment about the case of the printed font ($p < .01$; See Fig. 6). Similarly, there was more signal in left prefrontal cortex during encoding for words subsequently remembered than those subsequently forgotten ($p < .06$). The expected specificity was shown as these effects of condition were not found for medial frontal or right frontal regions, showing the specificity of word list learning as others have shown (Brewer et al., 1998).

Diffusion tensor imaging (DTI): The fractional anisotropy (FA) measure of DTI assesses brain white matter integrity. We examined whether FA values were differentially related to age in each group. In addition we compared FA in specific brain regions across groups. For this latter comparison, we included previously obtained data from a prior study on a group of men who were not on ADT to increase the N. For both of these analyses, regions of interest were placed in white matter in the genu and splenium of the corpus callosum, as well as prefrontal and occipital white matter.

As others have shown, whole brain FA decreases with age, with all groups combined ($p = .02$) but no specific region showed an age-related decline. FA values marginally declined with increasing age in men on ADT ($p = .08$) but not in the men who were not on ADT. ADT did not differentially affect FA values with aging in any particular region (genu or splenium of the corpus callosum, prefrontal cortex, occipital lobe) however, the FA value of the splenium region marginally increased with aging in men who were not on ADT ($p = .10$). No differences between men who were on short versus long term ADT were found in the three group analysis. However, men newly on ADT showed significantly lower FA values with age in the whole brain and genu ($p < .05$) but not the other regions. However, the very small numbers of men in the new ADT group suggest these regression findings should be viewed with caution.

Men on ADT had lower whole brain FA values than men who were not on ADT ($p < .01$; Fig. 7). This was true of only the occipital region ($p < .01$), as no other regions differed between groups. In the three group analysis, there were no group differences in the whole brain FA, prefrontal cortex, genu or splenium but the new ADT men had lower FA values in the occipital lobe than those men not on ADT and both ADT groups had lower FA values in the occipital lobe than the men who were not on ADT ($p < .05$).

Quantitative T1 (QT1): A automated method was developed to mask and segment tissue for QT1 analysis. No significant effects were found between men on ADT and men who were not on ADT nor were there differences between those early versus later in their course of treatment. QT1 analyses showed the expected age-related increase in T1 in both white and grey matter over all the groups and there were no group differences (see Fig 8).

KEY RESEARCH ACCOMPLISHMENTS

- Neither men on ADT nor those not on ADT met the criteria for early Alzheimer's disease. This is in contrast to other studies that showed memory impairment in men on ADT when contrasted to men who do not have prostate cancer.
- While still in the clinically normal range, men on ADT report more depression than men who are not on ADT. Additional data (POMS, FAQ, FACT-P) suggests malaise is particularly difficult for the men early in ADT treatment.
- Men on ADT report feeling more confused than men not on ADT regardless of length of treatment.

- This study demonstrated the use of multiple forms of neuroimaging to examine potential neurotoxicity of ADT
- Brain activity did not differ between men who were or were not on ADT
- White matter integrity, particularly in the occipital region does appear to be lower in men on ADT.
- Quantitative T1 shows an expected age-related increase in both grey and white matter, but ADT does not affect this magnetic resonance measure of macromolecular structure.

REPORTABLE OUTCOMES

Roalf, DR, Berlow, YA, Lebow, MR, Salat, DH, Beer, TM, Janowsky JS. Brain diffusion tensor imaging shows white matter loss in men with prostate cancer (*manuscript was revised but rejected from multiple journals and not resubmitted*)

Young L.A., Lebow, M.R, Roalf, D.R., Beer, T.M., & Janowsky, J.S. Prefrontal activity does not reflect androgen deprivation induced memory impairment. Society for Neuroscience Annual Meeting. October 2009.

Roalf, D.R., Berlow, Y.A., Lebow, M.R., Young, L.A., Salat, D.H., & Janowsky, J.S. The effect of androgen deprivation on prefrontal white matter. 15th Annual Meeting of the Organization for Human Brain Mapping. June 19, 2009; San Francisco.

Grants Submitted:

Mechanisms for sex steroid effects on cognition in aging – NIH ROI 7/2008 (not funded)
Renewal of OHSU Cancer Center Grant (participant) 8/09

CONCLUSION: Overall, there was little evidence for androgen induced neurodegeneration, or androgen induced progression or acceleration of age-related decline. The source of the complaints by men on ADT concerning memory is still not clear, although malaise that includes mild depression is likely a contributing factor. There are many aspects of memory and cognition that were not addressed by this study, and thus the general feeling of cognitive impairment could arise from true cognitive impairments that were not studied. Finally, while we accomplished the aims of this study, to use advanced neuroimaging to examine ADT effects, the nature of the treatment, particularly early on in treatment makes the study of these men difficult. In particular, treatment starts and stops based on nonneurologic complications of treatment and aging, and men in this age range have a high rate of incidental MRI findings, which preclude accurate analysis of their images. Thus, recruitment and maintenance of men for all aspects of the study is particularly difficult. This was a preliminary study, however, that showed feasibility, but sufficient subjects for reliable analyses of the many relevant measures was not achieved.

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APPENDICES - SUPPORTING DATA (figures/tables)

Fig. 1 Men on either long or short-term ADT are more depressed than those not on ADT

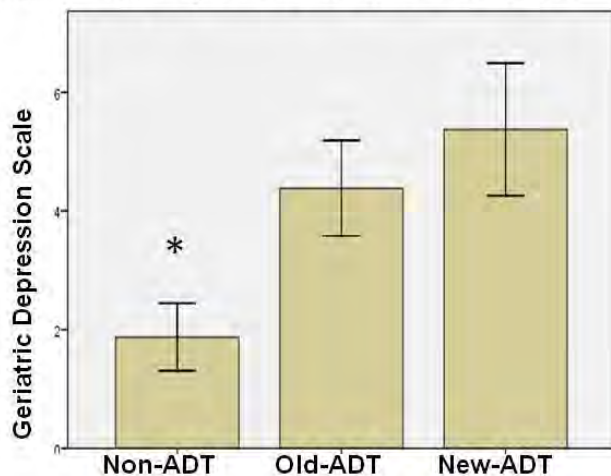


Fig. 2

ADT did not affect memory: Paragraph Recall

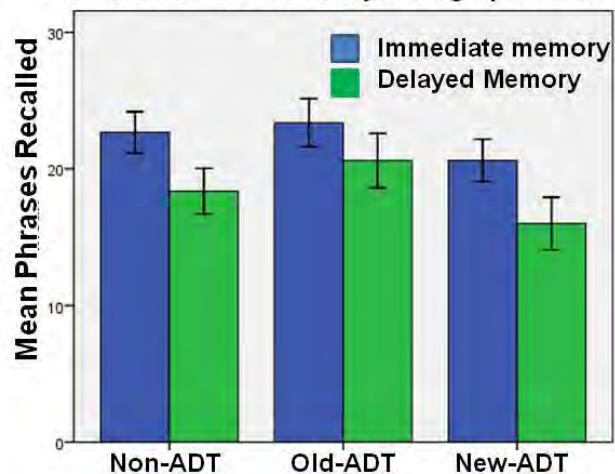
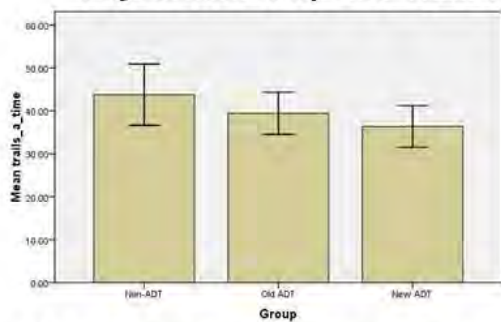


Fig 3 ADT did not affect Psychomotor Speed: Trails A



ADT did not affect cognitive flexibility: Trails B-A

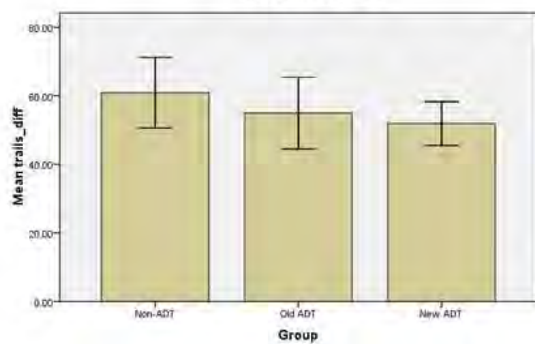


Fig. 4 Men on ADT reported more confusion than those not on ADT

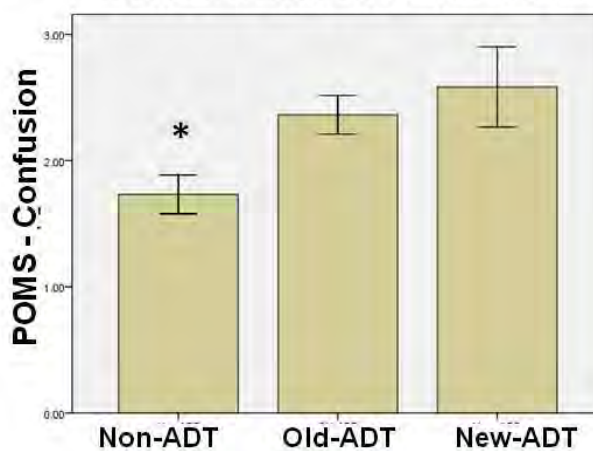


Fig. 5

Men newly on ADT report more functional deficits than those on long term ADT or those not on ADT.

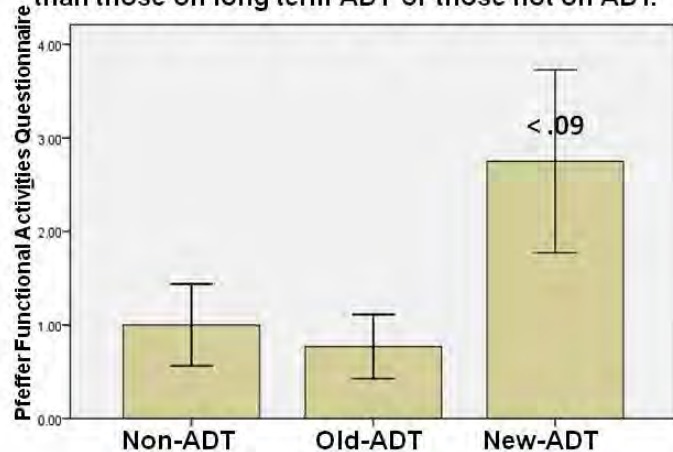


Fig. 6

Men newly on ADT report poorer quality of life than men on long term or those not on ADT

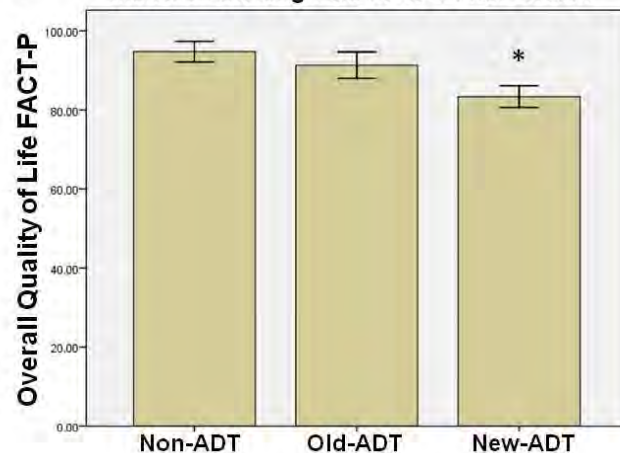


Fig. 7

Example Regions of Interest
(radiologic convention, Rt/Lft reversed)

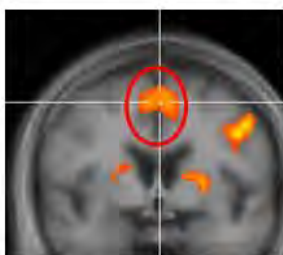
Right Frontal



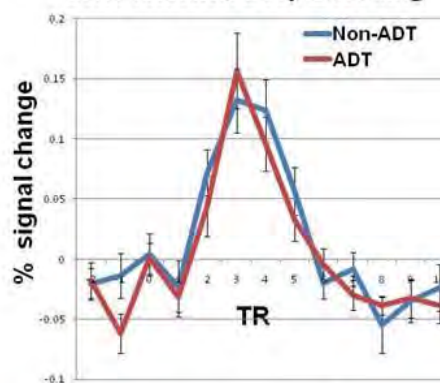
Left Frontal



Medial Frontal



Left Prefrontal Deep Encoding



Left Prefrontal – Activity for Items Remembered

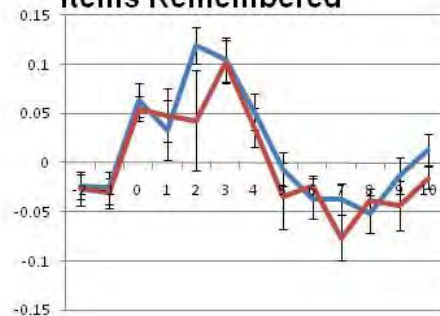


Fig. 8 Men on ADT have lower occipital FA white matter values

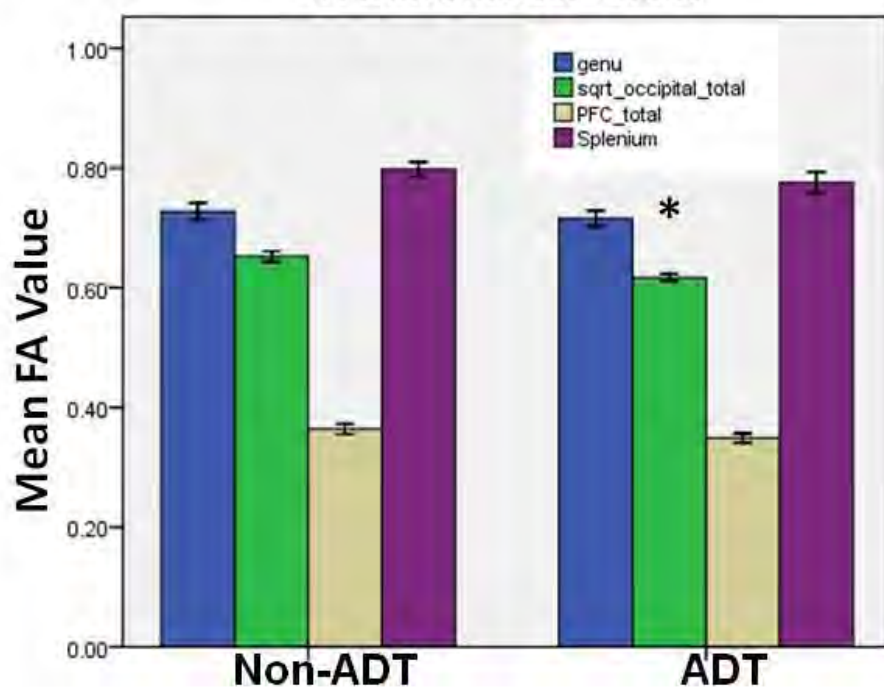


Fig. 9 QT_1 Analysis: T1 increases with age, but is not affected by ADT

